

active in this case.

REQUEST FOR RECONSIDERATION

Applicants wish to thank Examiner Hartley for the helpful and courteous discussion conducted with their U.S. representative on June 21, 2000. In accordance with the remarks made during the discussion, Applicants have modified the claims in order to clarify the present invention. Applicants now wish to make the following additional remarks.

As noted previously, in order to deliver drugs across the blood brain barrier of mammals, the conventional wisdom is that it is necessary to use nanoparticles to which drugs are complexed (incorporated or adsorbed) and which nanoparticles are surrounded by a coating made of an appropriate surfactant. See, for example, Kreuter et al (WO 95/22963), described at page 1 of the present specification. Quite surprisingly, it has now been discovered that effective nanosphere drug targeting systems can be provided, which do not require an outer coating of surfactant, and which can, therefore, be produced much more simply.

In particular, the present invention provides, in part, a drug targeting system for administration to a mammal, which contains:

a) nanoparticles made of a polymeric material, the nanoparticles being free of a surfactant surface coating and containing the polymeric material, one or more physiologically effective substances to be delivered to the mammal and one or more stabilizers for the nanoparticles allowing targeting of the physiologically effective substances to a specific site within or on a mammalian body;

wherein the stabilizers are selected from the group consisting of polysorbate 85, polysorbate 81, dextran 12,000, carboxylic acid esters of glycerol, sorbitan monostearate,

sorbitan monooleate, polyoxamer 188, polyoxamines, alkoxyated ethers, alkoxyated esters, alkoxyated mono-, di- and triglycerides, alkoxyated phenols and diphenols, the Genapol compounds, Bauki compounds, sodium stearate, metal salts of alcohol sulfates, metal salts of sulfosuccinates and mixtures of two or more of these substances; and

b) a physiologically acceptable carrier, which allows transport of the nanoparticles to the target within said mammal after administration.

Claims 41-83 stand rejected under 35 U.S.C. §102(b) as being anticipated by Hyon (EP 330180). However, this reference fails to either disclose or suggest the present invention.

In particular, and as noted previously, the emulsifying agents of Hyon are generally used to stabilize the emulsion therein, which is either an O/O type emulsion or a W/O type emulsion. That is, Hyon teaches the use of any conventional emulsifying agent as long as it is capable of forming a stable O/O or W/O type emulsion. Notably, this reference specifically teaches that:

For facilitating the formulation, an emulsifying agent is preferably employed. The emulsifying agent includes any conventional emulsifying agents insofar as they can form a stable O/O or W/O type emulsion . . . see page 5, lines 40-42.

For example, Example 1 at page 6 of Hyon teaches the use of "Span 80" as an emulsifier in the preparation of an emulsion. Attention is directed to page 1083 of Hawley's Condensed Chemical Dictionary (11th Edition) which defines "Span" as fatty acid partial esters of sorbitol anhydrides (or sorbitan).

Several comments are worthy of note.

First, Hyon clearly utilize a specific class of surfactants to produce an emulsion. Hyon is not at all concerned with any medicinal effect arising from the use of the emulsifier in the subsequent dry formulation.

Second, although Applicants concede, as noted by the Examiner from page 4, lines 46-54 of Hyon, that the polymer nanoparticles of Hyon, themselves, may contain the "other pharmaceutically acceptable substances," it is emphasized that these other substances are necessarily "pharmaceutically acceptable" which means "inert" and having no effect on the active ingredients contained therewith.

Third, Hyon fails to disclose or suggest the specific stabilizers of the present invention. Notably, Hyon teaches specifically the possible use of polyoxyethylene sorbitan monolaurate. The term "monolaurate" denotes a monolaurate group which is a C₁₂ saturated group of the formula CH₃(CH₂)₁₀COO-.

In contrast, the closest convergence of the presently claimed stabilizers to this compound is 1) polysorbate 81 (polyoxyethylene sorbitan monoleate), wherein monoleate denotes the unsaturated C₁₇ group of the formula CH₃(CH₂)₇CH=CH(CH₂)₇COO-, 2) polysorbate 85 (polyoxyethylene sorbitan trioleate, denoting three of the above groups, and 3) sorbitan monoleate and sorbitan monostearate. Monostearate denotes the saturated C₁₈ group of the formula CH₃(CH₂)₁₆COO-. See Attachment 1 to this amendment and pages 685, 854 and 1091 of Hawley's, id.

Thus, it is clear that Hyon would fail to put one skilled in the art in possession of the present invention.

Finally, in view of Kreuter et al, discussed below, one skilled in the art would be taught to use a surfactant coating for nanoparticles in order to have the active ingredients contained therein cross the blood brain barrier. Thus, Kreuter et al teach away from the present invention.

Hence, this ground of rejection is unsustainable and should be withdrawn.

Claims 41-87 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Kreuter

et al (WO 95/22963), Canal (EP 486959), Dyatlov (WO 94/15590) or Hyon (EP 330180).

However, none of these references, either alone or in combination, describes or suggests the present invention.

In particular, Kreuter et al, as noted at page 1 of the present specification, necessarily teach the use of a surfactant coating on the nanoparticles thereof. Quite clearly, the present invention avoids the use of the surfactant coating. In fact, one of the principle objects of the present invention is the avoidance of such a surfactant surface coating on the nanoparticles.

Notably, Kreuter et al describe the preparation of nanoparticles "in conventional ways". See the Abstract. The nanoparticles are "then coated with additional surfactant and given to the body of animals or humans". See the Abstract. Thus, the nanoparticles of this reference are clearly characterized by the presence of an outer coating of surfactant.

Moreover, the stated reason for using this outer coating of surfactant is to allow "drugs or diagnostic agents to cross the blood-brain barrier (bbb)". See the Abstract. Kreuter et al describe the many conventional approaches which have been used to allow administered drugs to cross the blood-brain barrier. See pages 2-5 thereof. In contrast thereto, Kreuter et al teach that their invention:

... is based on the surprising finding that treatment of nanoparticles having a drug absorbed, adsorbed or incorporated therein with a sufficient coating of an appropriate surfactant allows the adsorbed drug to traverse the bbb. See page 6 thereof.

Further, Kreuter et al teach that:

The critical, innovative step is that after drug absorption or incorporation, the nanoparticles are coated with surfactants by incubating them in a surfactant solution under appropriate conditions. The surfactant allows penetration of the bbb by the drug without physical modification of the nanoparticle or the drug itself. See page 7 thereof.

In contrast, the present invention surprisingly avoids the use of the outer coating of surfactant as taught by Kreuter et al. See pages 3 and 4 of the present specification. Clearly, in view of the teachings of Kreuter et al., one skilled in the art would have no motivation to avoid the use of the outer coating of surfactant, as without the coating, one skilled in the art would not expect administered drugs to cross the blood-brain barrier as in the present invention.

Furthermore, the particular stabilizers used in accordance with the present invention are readily distinguishable from the substances used in Dyatlov et al and Canal et al. Notably, the present invention uses specific stabilizers which are neither disclosed nor suggested by either of these cited references.

Further, the emulsifying agents of Hyon et al are merely used to stabilize the emulsion therein, which is either a O/O type emulsion or a W/O type emulsion. That is, Hyon et al clearly teach the use of any conventional emulsifying agent insofar as they are able to form a stable O/O or W/O type emulsion. Thus, the stabilizer of Hyon et al is a stabilizer of the emulsion and is clearly not incorporated into a nanoparticle. In contrast, the stabilizer of the present invention is incorporated into the polymer of the nanoparticle for stabilization in order to obtain the desired targeting of the nanoparticles to or on specific targets in or on the mammalian body without using the outer surfactant coating of Kreuter et al.

Quite clearly, one skilled in the art would not be put in possession of the present invention even from the combined teachings of these references.

Hence, this ground of rejection is believed to be unsustainable and should be withdrawn.

Claims 48, 68 and 70 stand rejected under 35 U.S.C. §112, first paragraph.

However, in view of the above amendments, this ground of rejection is believed to be moot.

Claims 41, 50, 48, 54, 55, 68, 70 and 72 stand rejected under 35 U.S.C. §112, second paragraph.

However, in view of the above amendments, this ground of rejection is believed to be moot.

Also, Applicants attach to this response page 36, of the original application, containing an Abstract, which appears to be missing from the Official Patent Office file.

Applicants also respectfully assert that diagnostic substances used in nuclear medicine and radiation therapy are well known to those skilled in the art. Hence, it is respectfully submitted that Claims 97, 119 and 120 are proper.

Additionally, it is pointed out that the term "alkoxylated esters" clearly does not include the polyoxylated sorbitan monolaurate of the prior art inasmuch as sorbitan monolaurate is a tri-hydroxylated ester. See attached "Enclosure 1", and the term "oxylated" is an old, well-established and still used standard designation for "hydroxylated", "epoxylated" and "oxo-substituted" (keto and aldehyde groups), as may be readily seen in standard textbooks. Consequently, poly-oxylated sorbitan monolaurate is a poly-hydroxylated ester, an epoxylated ester, an oxo-substituted ester or a combination thereof which clearly distinguishes it from "alkoxylated esters". Thus, it is clear that one skilled in the art would understand "polyoxylated sorbitan monolaurate" to be "poly-hydroxylated sorbitan monolaurate" or "epoxylated sorbitan monolaurate" or "oxo-substituted sorbitan monolaurate". "Enclosure 1" - referred to above - is provided in order to afford some information about sorbitan esters from the Merck Index to support this thesis.

Furthermore, also attached are "Enclosures 2 to 4" concerning chemical definitions of

"Genapol" and "Bauki" compounds. The attached "Enclosures 2 to 4" were found on the "world wide web" and the structures may be seen from the shortened formulae. By way of examples C12E10 for Genapol C-100 is translated to be " $\text{CH}_3(\text{CH}_2)_{11} \text{O}(\text{CH}_2\text{CH}_2\text{O})_{10}\text{H}$ ", i.e., 12 C atoms of an alkyl chain plus 10 ethylene glycol units, which, in fact, can be readily checked with the molecular weight in the second column.

The Bauki surfactants are named according to the first letters of the surnames of the two German inventors Kurt H. Bauer and Markus Kiefer. The structures are described in U.S. Patent No. 5,576,012, the first page of which is attached as "Enclosure 5".

Finally, also attached to this amendment, is a list of generic chemical definitions for the terms queried by the Examiner.

Accordingly, in view of all of the above amendments and attendant remarks, it is believed that the present application now stands in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Norman F. Oblon
Attorney of Record
Registration No. 24,618

William E. Beaumont
Registration No. 30,996



22850

(703) 413-3000
Fax #: (703) 413-2220
NFO/WEB:kst

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IN THE CLAIMS

--Claims 41-87 (Cancelled).

Claims 88-134 (New).--

Enclosure 1

8871

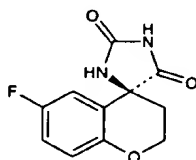
Sorbinil

Long needles. Agreeable odor of new mown grass. mp 30.5-31.5°. bp₁₂ ~80°. Volatile with steam. Insol in water. Sol in alcohol, ether, oils. Not stable to air; must be sealed in evacuated ampuls for storage.

Diphenylurethan, C₁₉H₁₉NO₂, crystals from petr ether. mp 78-79°.

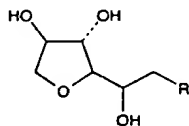
3,5-Dinitrobenzoate, yellowish needles from petr ether. mp 85°.

8871. Sorbinil. (S)-6-Fluoro-2,3-dihydrospiro[4H-1-benzopyran-4,4'-imidazolidine]-2',5'-dione; (+)-(4S)-6-fluoro-spiro[chroman-4,4'-imidazolidine]-2',5'-dione; CP-45634. C₁₁H₈FN₂O₃; mol wt 236.20. C 55.94%, H 3.84%, F 8.04%, N 11.86%, O 20.32%. Spirohydantoin aldose reductase inhibitor. Prepn of racemate and resolution of isomers: R. Sarges. Ger. pat. 2,821,966; *idem*, U.S. pat. 4,130,714 (both 1978 to Pfizer). Synthesis: R. Sarges *et al.*, *J. Org. Chem.* 47, 4081 (1982); N. L. Dirlam *et al.*, *J. Org. Chem.* 52, 3587 (1987). Absolute configuration: R. Sarges *et al.*, *J. Med. Chem.* 28, 1716 (1985). Effect on polyol accumulation in diabetic rats: M. J. Peterson *et al.*, *Metabolism* 28, Suppl. 1, 456 (1979). Pharmacokinetics in humans: G. Foulds *et al.*, *Clin. Pharmacol. Ther.* 30, 693 (1981). HPLC determ in human lens and plasma: P. Lloyd, M. J. C. Crabbe, *J. Chromatog.* 343, 402 (1985). Preliminary clinical trials in diabetic neuropathy: R. J. Young *et al.*, *Diabetes* 32, 938 (1983); J. Jaspan *et al.*, *Lancet* 2, 758 (1983). Symposium on pharmacology and clinical efficacy: *Metabolism* 35, Suppl 1, 1-121 (1986).



Crystals from ethanol. mp 241-243°. [α]_D²⁵ -54.0° (c = 1 in methanol).

8872. Sorbitan Esters. Sorbitan fatty acid esters: SFAE. Nonionic surface active agents: partial esters of the common fatty acids (lauric, palmitic, stearic, and oleic) and hexitol anhydrides derived from sorbitol. Commercial products may be mixtures of fatty acid esters of 1,4- and 1,5-anhydrosorbitol and 1,4,3,6-dianhydrosorbitol, but generally conform to the structure depicted below. Prepn: K. R. Brown, U.S. pat. 2,322,820 (1943 to Atlas Powder Co.). Improved process: G. J. Stockburger, U.S. pat. 4,297,290 (1981 to ICI). Comprehensive description: P. Becher, "Polyol Surfactants" in *Nonionic Surfactants*, M. J. Schick, Ed. (Dekker, New York, 1967) pp 247-299. Description of prepn and uses: L. R. Chislett, J. Walford, *Int. Flavours Food Addit.* 7, 61 (1976). GLC determ of sorbitan monolaurate in plasma: S. H. Giovanetto, *Anal. Letters* 16, 867 (1983). Analysis by HPLC: N. Garti *et al.*, *J. Am. Oil Chem. Soc.* 60, 1151 (1983). Series of toxicity studies: *Food Cosmet. Toxicol.* 16, 519-542 (1978). Review: Cosmetic, Toiletory and Fragrance Assoc., *J. Am. Coll. Toxicol.* 4, 65-121 (1985).



Sorbitan Laurate R = OOC(C₁₁H₂₃)
Sorbitan Stearate R = OOC(C₁₇H₃₅)
Sorbitan Oleate R = OOC(C₁₇H₃₃)

Polyoxyethylene derivatives, see Polysorbates.

Sorbitan Laurate. C₁₉H₃₄O₆, sorbitan monolaurate, *Alkamuls SML*, *Arlacel 20*, *Emsorb 2515*, *Glycomul L*, *Span 20*. Yellow liquid. Acid value: <8. Saponification value: 150-165. Hydroxyl value: 330-360. Sol in mineral oil, cotton-

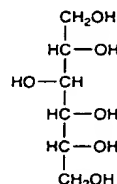
seed oil, methanol, ethanol, isopropyl alc, ethylene glycol. Insol in water, propylene glycol.

Sorbitan Stearate. C₂₄H₄₀O₆, sorbitan monostearate, *Alkamuls SMS*, *Arlacel 60*, *Glycomul S*, *Span 60*. White to tan waxy solid, mp 49-65°. Acid value: 5-11. Saponification value: 140-157. Hydroxyl value: 230-260. Sol in alcohols, carbon tetrachloride, toluene. Insol in water, acetone, mineral spirits.

Sorbitan Oleate. C₂₄H₄₀O₆, sorbitan monooleate, *Alkamuls SMO*, *Arlacel 80*, *Capmul O*, *Emsorb 2500*, *Glycomul O*, *Span 80*. Yellow to amber colored oily liquid. Acid number: 5-8. Saponification value: 140-160. Hydroxyl value: 193-215. Sol in ethanol, isopropyl alc, mineral oil, vegetable oil. Insol in water, propylene glycol.

use: As emulsifiers, stabilizers, and thickeners in foods, cosmetics, and medicinal products. In the textile industry as fiber lubricants and softeners. Pharmaceutical aid (surfactant).

8873. Sorbitol. *D-Glucitol*; D-sorbitol; L-gulitol; sorbit; Cystosol; Resulax; Sorbilax; Sorbitur; Sorbo; Sorbostyl; Sorbilande. C₆H₁₄O₆; mol wt 182.17. C 39.56%, H 7.75%, O 52.70%. First found in the ripe berries of the mountain ash *Pyrus aucuparia* Ehrh. (L.) (*Sorbus aucuparia* L.), *Rosa-ceae*. Occurs also in many other berries (except grapes) and in cherries, plums, pears, apples, seaweed and algae. Has been detected in blackstrap molasses. Isoln from berries: Embden, Griesbach, *Z. Physiol. Chem.* 91, 268 (1914). Prepd industrially from glucose by high pressure hydrogenation or by electrolytic reduction: Boye, *Chem.-Ztg.* 82, 657 (1958); Fedor *et al.*, *Ind. Eng. Chem.* 52, 282 (1960); from dextrose by catalytic hydrogenation: Faith, Keyes & Clark's *Industrial Chemicals*, F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 774-778. Review of uses: Kempf, *Die Stärke* 6, 269-274 and 303-306 (1954); 9, 234-237 (1955).



Needles with 1/2 or 1H₂O. Sweet taste, ~60% as sweet as sugar (w/w). In the healthy human organism 1.0 g of sorbitol yields 3.994 calories which is comparable to 3.940 calories from 1.0 g of cane sugar. Seventy percent of orally ingested sorbitol is converted to CO₂ without appearing as glucose in the blood: Adcock, Gray, *Biochem. J.* 65, 554 (1957). The hydrated crystals melt somewhat below 100°. When completely anhyd mp 110-112°. [α]_D²⁰ -2.0° (H₂O). In the presence of molybdate the rotation is reversed and increased to +56°. Freely sol in water (up to 83%). High % sorbitol solns are much more viscous than corresp glycerol solns. Quite sol in hot alcohol, sparingly sol in cold alcohol. Also sol in methanol, isopropanol, butanol, cyclohexanol, phenol, acetone, acetic acid, DMF, pyridine, acetamide solns. Practically insol in most other organic solvents. Not attacked in the cold when mixed with dil acids, alkalies or mild oxidizing substances. Ka at 17.5° = 2.5 × 10⁻¹⁴. pH about 7.0. A commercial 70% aq soln may have the following characteristics: d₂₀²⁰ 1.2879; n_D²⁰ 1.45831; [α]_D²⁰ -2.10°; bp₇₆₀ 105°; pH between 6 and 7; viscosity (25°): 110 cp. d₂₀²⁰ for various % solns: 5% 1.014; 10% 1.038; 25% 1.099; 50% 1.198; 60% 1.249; 70% 1.299; 83% 1.391. Viscosity in cp at 20°: 5% soln 1.230; 10% 1.429; 25% 2.689; 50% 11.09; 60% 35.73; 70% 185; 83% > 10,000.

USE: In manuf of sorbose, ascorbic acid, propylene glycol, synthetic plasticizers and resins: as humectant (moisture conditioner) on printing rolls, in leather, tobacco. In writing inks to insure a smooth flow and to prevent crusting on the point of the pen. In antifreeze mixtures with glycerol or glycols. In candy manuf to increase shelf life by retarding the solidification of sugar; as humectant and softener in shredded coconut and peanut butter; as texturizer in foods;

D

Enclosure 2

1432 gen

land: CRC 1974; Schormüller, S. 501–521; Torrey, Dehydration of Fruits and Vegetables, Park Ridge: Noyes 1974; Tressler u. Woodroof, Fruit, Vegetable and Nut Products, Westport: Avi 1976; White, Nutritional Qualities of Fresh Fruits and Vegetables, Mount Kisco: Futura 1974; Winnacker-Küchler (3.) 3: 523–529; zahlreiche weitere Publikationen erscheinen bei Avi (Westport); s. a. die einzelnen G.-Sorten u. *Fruchtsäfte; ältere Lit. s. 7. Aufl. dieses Werkes.

... **gen** (von griech.: genes = verursachend, verursacht). Suffix in wissenschaftlichen Bez., das eine „etwas erzeugende“ od. „aus etwas erzeugte“ Eig. andeuten soll; *Beisp.*: Pyrogene (machen Fieber), Kollagen (Leimbildner), Hydrogen (Wasserbildner), exogen (von außen eingeführt). – *E*...gen – *F*...gène

Genagen®. Fettsäurealkanolamidpolyglykol-ether (G. CA-050) als grenzflächenaktiver Waschrohstoff bzw. Ölsäurepolyglykolester (G. O-150) als nichtion. Sammler für die Erzflotation.

B.: Hoechst.

Genakor®. Kautschuk- u. Kunststoffauskleidungen als Oberflächenschutz für App., Behälter, Armaturen u. Rohrleitungen.

B.: Kalle.

Genamin®. Tensidrohstoffe auf der Basis von Fettaminen, deren Polyglykolethern u. quartären Ammoniumverbindungen.

B.: Hoechst.

Genaminox®. Alkyldimethylaminoxid als nichtion. Tensid von Hoechst.

Genantin®. Gefrierschutzmittel auf Glykolbasis von Hoechst.

Genapol®. Wasch-, Netz- u. Dispergiermittel auf der Basis von Alkylpolyglykolethern u. Ethylenoxid-Propylenoxid-Blockpolymeren bzw. kosmet. Rohstoffe auf Basis Alkylpolyglykolethersulfat, Alkylsulfat u. Fettsäureglykolestern, auch mit seiden- od. perlglanzgebenden Zusätzen.

B.: Hoechst.

Genauigkeit. Beim *Messen versteht man unter G. stets die Differenz zwischen einem Ergebnis (od. einem Mittelwert) u. dem wahren Wert der zu bestimmenden Größe, unter *Präzision* dagegen die Abweichungen unter den Ergebnissen, d. h. deren Streuung. G. gibt also den Grad der *Näherung*, die Präzision den Grad der *Reproduzierbarkeit bei Best. u. Messungen an. – *E* accuracy

Lit.: Compilation of ASTM Standards on Precision and Accuracy for Various Applications, Philadelphia: ASTM 1977; DIN 1319, T3 (Jan. 1972); Eisenhart, Science 160 (1968) 1201; Kateman u. Pijpers, Quality Control in Analytical Chemistry, New York: Wiley 1981; Ku, Precision Measurement and Calibration, Washington: Nat. Bur. Standards 1969; Pharm. Biol. 4: 58–60; Pure Appl. Chem. 53 (1981) 1805–1825; Reproducibility and Accuracy of Mechanical Tests (STP 626), Philadelphia: ASTM 1977; Tölg, Naturwiss. 63 (1976) 99–110; s. a. *Messen.

Genchirurgie s. *Gene u. *Gentechnologie.

Gene. Von Johannsen (1909) geprägter u. von griech.: genos = Geschlecht, Gattung, Nachkommenschaft abgeleiteter Begriff für die Erbanlagen der Lebewesen. Im Sinne der klassischen *Genetik (Vererbungslehre) sind G. biolog. Einheiten, die in den *Chromosomen lokalisiert u. durch die Fähigkeit zur Merkmalsauslösung, zur identischen Reproduktion u. zur Mutation definiert sind. Die *Merkmalsauslg.* läßt sich in zahlreichen Erbexperimenten nachweisen, bei denen man den Erbgang von Merkmalen wie Haar- u. Augenfarbe, Struktureigentümlichkeiten, Auftreten od. Fehlen von Stoffwechselpod. u. v. a. verfolgt u. dabei eine Vererbung dieser Merkmale nach bestimmten Gesetzmäßigkeiten registriert. Erste Experimente dieser Art stellte G. Mendel (1865) an, der die später nach ihm benannten Vererbungsgesetze formulierte. Die Fähigkeit zur *ident. Reproduktion* der G. läßt sich aus der *Reproduzierbarkeit der Erbexperimente ableiten u. aus der Tatsache, daß eine bestimmte Organismenspezies über lange Zeiträume u. Generationenfolgen in ihren Merkmalen konstant bleibt; ihre G. müssen sich also über diese Zeiträume oftmals *ident.* reproduziert haben. Weiter führen diese Überlegungen zu dem Schluß, daß die G. in den Chromosomen lokalisiert sind; denn diese sind diejenigen Organellen der *Zellen (vgl. die Abb. dort), die bei jeder Zellteilung von Generation zu Generation weitergegeben werden (s. *Mitose). Genet. Material findet sich jedoch nicht nur im Zellkern, sondern auch in *Mitochondrien u. – in Pflanzen – in den *Plastiden, vgl. a. *Chloroplasten u. Wild (Umschau 76 (1976) 477–483). In relativ seltenen Fällen verändert sich ein G. plötzlich, es mutiert und wird in dieser veränderten Form weitervererbt – falls die Mutation nicht letal ist (Crow, Spektrum Wiss. 1979, Nr. 4, S. 28–38). Solche *Mutationen* sind die Voraussetzung für die Entw. neuer Arten; sie können spontan, durch energiereiche *Strahlung (Ehling, Umschau 80 (1980) 754–759) u. durch Chemikalien entstehen (s. *Mutagene u. *Teratogene u. vgl. Bayer, Pharmazie uns. Zeit 8 (1979) 11–17). Verständlicherweise bemüht man sich, für züchterische u. a. wissenschaftliche Zwecke G. von äußeren Einfl. frei in sog. *Genbanken* aufzubewahren (Bass, Umschau 73 (1973) 229–232). Die *Molekularbiologie hat in den Forschungen der letzten 40 Jahre die *Desoxyribonucleinsäure (DNA) als Gensubstanz identifiziert. Ein G. ist ein bestimmter Abschnitt der DNA (bei einigen Viren auch der *Ribonucleinsäure, RNA), der durch seine spezif. Basensequenz die Synthese eines spezif. Proteins

Enclosure 3: see page 2

Properties of Detergents (Amphiphiles)

from Dr. Shaun D. Black (University of Texas Health Center at Tyler)

Non-ionic Detergents

Ionic Detergents

Zwitterionic Detergents

Footnotes

References

Non-Ionic Detergents						
Detergent Name †	Purity ‡	MW (monomer)	CMC (mM)§	CMC Conditions	Aggregation #	MW (micelle)
APO-10	M	218.3	4.6	50 mM Na ⁺	131	28,597
APO-12	M	246.4	0.568	50 mM Na ⁺	2232	549,965
BRIJ-35 (C ₁₂ E ₂₃)	M	1200 (avg)	0.09	50 mM Na ⁺	40	
C ₈ E ₆	M		9.9	25° C	32	13,000
C ₁₀ E ₆	M	427.1	0.9	50 mM Na ⁺	40	17,084
C ₁₀ E ₈	M	515.1				
C ₁₂ E ₆	M	451.1	0.087	50 mM Na ⁺		
C ₁₂ E ₈ (Atlas G2127)	M	539.1	0.11	50 mM Na ⁺	123	66,309
C ₁₂ E ₉	M	583.1	0.08	50 mM Na ⁺		
C ₁₂ E ₁₀ (Brij 36T)	M		0.2			
C ₁₆ E ₁₂	M		0.0023	25° C	152	117,000
C ₁₆ E ₂₁	M		0.0039	25° C	70	82,000
Cyclohexyl- <i>n</i> -ethyl-β-D-Maltoside	M	452.5	120	50 mM Na ⁺		
Cyclohexyl- <i>n</i> -hexyl-β-D-Maltoside	M	508.6	0.56	50 mM Na ⁺		
Cyclohexyl- <i>n</i> -methyl-β-D-Maltoside	M	438.5	340	50 mM Na ⁺		
<i>n</i> -Decanoylsucrose	M	496.6	2.5	50 mM Na ⁺		
<i>n</i> -Decyl-β-D-glucopyranoside	M	320.4	2.2	50 mM Na ⁺		
<i>n</i> -Decyl-β-D-maltopyranoside	M	482.6	1.6	50 mM Na ⁺		
<i>n</i> -Decyl-β-D-thiomaltoside	M	498.6	0.9	50 mM Na ⁺		
Digitonin	M	1229.3			60	70,000
<i>n</i> -Dodecanoyl	M	524.6	0.3			

sucrose				50 mM Na ⁺		
<i>n</i> -Dodecyl-β-D-glucopyranoside	M	348.5	0.13	50 mM Na ⁺		70,000
<i>n</i> -Dodecyl-β-D-maltoside	M	348.5	0.15	50 mM Na ⁺	98	70,000
Genapol C-100	P	627 (avg)				50,000
Genapol X-80	P	553 (avg)	0.06-0.15	50 mM Na ⁺		
Genapol X-100	P	641 (avg)	0.15	50 mM Na ⁺	88	56,000
HECAMEG	M	335.4	19.5	50 mM Na ⁺		
Heptane-1,2,3-triol	M	148.2				
<i>n</i> -Heptyl-β-D-glucopyranoside	M	278.3	79	50 mM Na ⁺		
<i>n</i> -Heptyl-β-D-thioglucopyranoside	M	294.3	30	50 mM Na ⁺		
LUBROL PX	P	582	0.006	50 mM Na ⁺	110	64,000
MEGA-8 (Octanoyl-N-methylglucamide)	M	321.5	58	50 mM Na ⁺		
MEGA-9 (Nonanoyl-N-methylglucamide)	M	335.5	19-25	50 mM Na ⁺		
MEGA-10 (Decanoyl-N-methylglucamide)	M	349.5	6-7	50 mM Na ⁺		
<i>n</i> -nonyl-β-D-glucopyranoside	M	306.4	6.5	50 mM Na ⁺		
Nonidet P-10 (NP-10)	P					
Nonidet P-40 (NP-40)	M	603.0	0.05-0.3	50 mM Na ⁺	100-155	
<i>n</i> -Octanoyl-β-D-glucosylamine (NOGA)	M	305.4	80	50 mM Na ⁺		
<i>n</i> -Octanoyl sucrose	M	468.5	24.4	50 mM Na ⁺		
<i>n</i> -Octyl-α-D-glucopyranoside	M	292.4	20			
<i>n</i> -Octyl-β-D-glucopyranoside	M	292.4	25	50 mM Na ⁺	27	7,895
<i>n</i> -Octyl-β-D-maltopyranoside	M	454.5	23.4	50 mM Na ⁺		
PLURONIC F-68	P	8400 (avg)				
PLURONIC F-127	P	12,600 (avg)				
THESIT		583	0.1	50 mM Na ⁺		
TRITON X-100 (<i>tert</i> -C ₈ -O-E _{9.6} like NP-40)	P	650 (avg)	0.3	50 mM Na ⁺	140	90,000
TRITON X-100 hydrogenated	P	631 (avg)	0.25	50 mM Na ⁺		

TRITON X-114 (<i>tert</i> -C ₈ -Ø-E ₇₋₈)	P	537 (avg)	0.35	50 mM Na ⁺		
TWEEN 20 (C ₁₂ ⁻ sorbitan-E ₂₀ ; Polysorbate 20)	P	1228 (avg)	0.059	50 mM Na ⁺		
TWEEN 40 (C ₁₆ ⁻ sorbitan-E ₂₀)	P		0.027			
TWEEN 60 (C ₁₈ ⁻ sorbitan-E ₂₀)	P		0.025			
TWEEN 80 (C _{18:1} ⁻ sorbitan-E ₂₀)	P	1310 (avg)	0.012	50 mM Na ⁺	58	75,980
<i>n</i> -Undecyl-β-D-maltoside	M	496.6	0.59	50 mM Na ⁺		

Ionic Detergents						
Detergent Name †	Purity ‡	MW (monomer)	CMC (mM)§	CMC Conditions	Aggregation #	MW (micelle)
Caprylic acid, Na ⁺ salt (<i>n</i> -octanoate)	M	166.2	351			
Cetylpyridinium chloride	M	274.0	0.90			
CTAB (Cetyltrimethylammonium bromide)	M	364.5	1.0	50 mM Na ⁺	170	62,000
Cholic acid, Na ⁺ salt	M	430.6	4	50 mM Na ⁺	3	1200
Decanesulfonic acid, Na ⁺ salt	M	244.3	32.6			
Deoxycholic acid, Na ⁺ salt (DOC)	M	414.6	1.5	50 mM Na ⁺	5	2000
Digitonin	P	1229	0.087		60	70,000
Dodecyltrimethylammonium bromide	M	308.4	14			
Glycocholic acid, Na ⁺ salt	M	487.6	7.1	50 mM Na ⁺	2.1	1000
Glycodeoxycholic acid, Na ⁺ salt	M	471.6	2.1	50 mM Na ⁺	2.1	1000
Lauroylsarcosine, Na ⁺ salt (Sarkosyl)	M	293.4			2	900
Lithium <i>n</i> -dodecyl sulfate	M	272.3	6-8	50 mM Na ⁺		
Lysophosphatidylcholine (16:0)	M	495.7	0.007		186	92,000
Sodium <i>n</i> -dodecyl sulfate (SDS, Lauryl sulfate, Na ⁺ salt)	M	288.5	2.30	50 mM Na ⁺	84	24,200
Taurochenodeoxy-	M	521.7				

cholic acid, Na ⁺ salt						
Taurocholic acid, Na ⁺ salt	M	537.7	3.3	20 mM Na ⁺	4	2150
Taurodehydrocholic acid, Na ⁺ salt	M	531.6				
Taurodeoxycholic acid, Na ⁺ salt	M	521.7	2.7	50 mM Na ⁺	8	4200
Tauroolithocholic acid, Na ⁺ salt	M	505.7				
Tauroursodeoxycholic Acid	M	521.7				
Tetradecyltrimethylammonium bromide (TDTAB)	M	336.4	3.5	30° C	81	27,000
TOPPS	M	350.5	4.5	50 mM Na ⁺		

Zwitterionic Detergents						
Detergent Name †	Purity ‡	MW (monomer)	CMC (mM)§	CMC Conditions	Aggregation #	MW (micelle)
BigCHAP	M	878.1	3.4	50 mM Na ⁺	10	8800
CHAPS	M	614.9	6-10	50 mM Na ⁺	10	6150
CHAPSO	M	630.9	8	50 mM Na ⁺	11	9960
DDMAU	M	397.7	0.13	50 mM Na ⁺		
EMPIGEN BB (N-Dodecyl-N,N-dimethylglycine)	M	272.0	1.6-2.1	50 mM Na ⁺		
Lauryldimethylamine oxide (LDAO, LDAO, Empigen OB)	M	229.4	1-3	50 mM Na ⁺	76	17,000
ZWITTERGENT 3-08	M	279.6	330	50 mM Na ⁺		
ZWITTERGENT 3-10	M	307.6	25-40	50 mM Na ⁺	41	12,600
ZWITTERGENT 3-12 (3-Dodecyl-dimethylammonio-propane-1-sulfonate)	M	335.6	2-4	50 mM Na ⁺	55	18,500
ZWITTERGENT 3-14	M	363.6	0.1-0.4	50 mM Na ⁺	83	30,200
ZWITTERGENT 3-16	M	391.6	0.01-0.06	50 mM Na ⁺	155	60,700

† BRIJ and TWEEN detergents are registered trademarks of ICI Americas, Inc.; EMPIGEN detergents are registered trademarks of Allbright and Willson; LUBROL is a registered trademark of Imperial Chemical; and ZWITTERGENT is a registered trademark of Calbiochem-Novabiochem Corporation.

‡ "Purity" refers to the "dispersity" of the detergent preparation. "P" indicates heterogeneity or polydispersity in molecular form, while "M" indicates homogeneity or monodispersity.

§ CMC refers to the Critical Micellar Concentration, or that total concentration of detergent that corresponds to the maximum possible concentration of detergent monomer in solution. The CMC is very sensitive to temperature and polarity of the medium. The CMC is generally given at 20-25° C, unless indicated otherwise in the table.

References: *Values in the table were taken from one or more of the following sources*

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Suggestions for additions or changes can be sent to Dr. Shaun D. Black



Last update June 16, 1998
Shaun D. Black, University of Texas Health Center at Tyler

014158 accesses since June 11, 1998.

Enclosure 4: ● e pages 4/5

Properties of Detergents

This list is still (and probably will be forever) under construction. At the moment it is a simple compilation of data taken from publications, catalogues etc. I have not remeasured the figures myself nor do I comment on them. The data for a particular detergent depend not only on environmental factors like ionic strength, temperature etc. but the published numbers differ also due to different methods of determining them (for instance ANSA-fluorescence and surface tension measurements for cmc, gelfiltration and small angle scattering for micellar size etc.)!

If you find any errors or if there are detergents missing in the list, please drop me an E-mail. Any comments are welcome!

The following detergent classes are listed below:

● Non-ionic Detergents

● 1 Sugar Derivatives

1.1 Alkyl Glucopyranosides

1.2 Alkyl Thio-glucopyranosides

1.3 Alkyl Maltopyranosides

1.3.1 Alkyl Thio-maltopyranosides

1.4 Alkyl Galactopyranosides

1.5 Alkyl Sucroses

1.6 Glucamides

● 2 Oligoethyleneglycol Derivatives

2.1 Alkyl Polyoxyethylenes

2.2 Phenyl Polyoxyethylenes

● 3 Dimethylamine-N-Oxides

● 4 Cholate Derivatives

● 5 n-Octyl Hydroxyalkylsulphoxides

● 6 Sulphobetaines

● 7 Lipid-like Detergents

7.1 Phosphocholine Compounds

● Zwitter-ionic Detergents

1 Bile Acids

● Ionic Detergents

Non-Ionic Detergents

1 Sugar Derivatives

1.1 Alkyl Glucopyranosides

Name	Molwt.	cmc/mM	cmc/%	AN	Mic.size/kD	Ref.
n-Hexyl- β -D-glucopyranoside (C6-GP)	264.3	250	6.6			[H]
C7-GP	278.3	79	2.2			[H]
C8-GP	292.4	17.4		~80		[C]
		30.3	0.89			#241
		23		78		[I]
		25			8	#220
		23.2, 13.5				#221
		34		27, 75	8, 20	[A]
		20-25		84		[H]
		24.5				[G]
		25.4	0.74	84	25	[E]
C9-GP	306.4	6.5	0.2			#241, [G]
C10-GP	320.4	2-3				[H]
		2.2	0.07			[G]
		4.2				[E]
C12-GP	348.5	0.19	0.007			[G]
		0.14				[E]
		0.13			70	[H]
n-Cyclohexyl-propyl- β -D-glucoside (Cyglu-3)	308.4	28				[G]
C8-glucosylamine (NOGA)	305.4	80	2.4			[H]

1.2 Alkyl Thio-glucopyranosides

Name	Molwt.	cmc/mM	cmc/%	AN	Mic.size/kD	Ref.
n-Heptyl- β -D-thioglucopyranoside (C7-tGP)	274.3	30	0.82			[H]
C8-tGP	308.4	9	0.28			[H]

1.3 Alkyl Maltopyranosides

Name	Molwt.	cmc/mM	cmc/%	AN	Mic.size/kD	Ref.
n-Octyl- β -D-maltopyranoside (C8-M)	454.5	23.4	1.06			[H]
C10-M	482.6	1.6	0.08			[H]

		1.8					[G]
		P.4					[E]
C11-M	496.6	0.59	0.03				[H]
⊗ C12-M	510.6	0.15	0.008				#241
		0.16		130	66		[I],235,[C]
		0.16-0.19			50		#220
		0.17					[G]
		0.1-0.6		98	70		[H]
		0.14	0.007	98	50.1		[E]
C13-M	524.6	0.033	0.002				[G]
C14-M	538.6	0.01	0.0005				[G]
Cyclohexyl-methyl-β-D-maltopyranoside (Cymal-1)	438.5	340	14.9				[G]
Cymal-2	452.5	120	5.4				[G]
Cymal-3	466.5	34.5	1.6				[G]
Cymal-4	480.5	7.6	0.37				[G]
Cymal-5	494.5	2.4	0.12				[G]
Cymal-6	508.5	0.56	0.03				[G]
Cymal-7	522.5	0.17					[G]

1.3.1 Alkyl Thio-maltopyranosides

Name	Molwt.	cmc/mM	cmc/%	AN	Mic.size/kD	Ref.
n-Octyl-β-D-thiomaltopyranoside (C8-tM)	308.4	9				[G]
C9-tM	484.6	3.2				[G]
C10-tM	498.6	0.9				[G]
C12-tM	512.7	0.2				[G]

1.4 Alkyl Galactopyranosides

Name	Molwt.	cmc/mM	cmc/%	AN	Mic.size/kD	Ref.
n-Octanoyl-β-D-galactopyranoside	292.4	29.5	⊗ 0.86			[G]

1.5 Alkyl Sucroses

Name	Molwt.	cmc/mM	cmc/%	AN	Mic.size/kD	Ref.
n-Octanoylsucrose	468.5	24.4	1.14			[H]
n-Decanoylsucrose	496.6	2.5	0.12			[H]
n-Dodecanoylsucrose	524.6	0.3	0.016			[H]

1.6.1 Glucamides

Name	Molwt.	cmc/mM	cmc/%	AN	Mic.size/kD	Ref.
MEGA-8	321.4	58	1.86			[H]
		79	2.54			[G]
MEGA-9	335.5	19-25				[H]

		25	0.84	[G]
MEGA-10	349.5	7	0.25	#241
		6-7		[G], [H]
⊗ HECAMEG	335.4	19.5	0.65	#224

1.6.2 Hydroxyethylglucamides

Name	Molwt.	cmc/mM	cmc/%	AN	Mic.size/kD	Ref.
Octanoyl-N-hydroxyethylglucamide (HEGA-8)	351.5	109				[G]
HEGA-9	365.5	39				[G]
HEGA-10	379.5	7.0				[G]
HEGA-11	393.5	1.4				[G]
Cyclohexylethanoyl-HEGA (C-HEGA-8)	349.5	277				[G]
C-HEGA-9	363.5	108				[G]
C-HEGA-10	377.5	35				[G]
C-HEGA-11	391.5	11.5				[G]

2 Oligoethyleneglycol Derivatives

2.1 Alkyl Polyoxyethylenes

Name	Molwt.	cmc/mM	cmc/%	AN	Mic.size/kD	Ref.
C5E1	132.2					[J]
C5E2	176.3					[J]
C5E3	220.3					[J]
C6E1	146.2					[J]
C6E2	190.3					[J]
C6E3	234.3	100	2.34			[J]
C6E4	278.4	90	2.51			[J]
C6E5	322.4	90	2.90			[J]
C7E3	248.4					[J]
C7E4	292.4					[J]
C7E5	336.5					[J]
C8E1	174.3	4.9	0.085			[J]
C8E2	218.3					[J]
C8E3	262.4	7.5	0.19			[J]
C8E4	306.4	7.2	0.22			[J]
⊗ C8E5	350.5	4.3	0.15			[C]
		6.0	0.21	32	11	#241, [E]
⊗ C8En (Octyl-POE, Rosenbusch-Tens.)						[J]
C10E1						[F]
C10E2						[F]
C10E3						[F]
C10E4	334.5	0.98 (10C)	0.033			[J]

		0.68 (25C)	0.023			[J]
C10E5	378.56	1.18 (10C)	0.045			[J]
		0.81 (25C)	0.031			[J]
C10E6	423	0.46		76	32	[E]
C10E7						[F]
C10E8	511	1.0				[D]
		0.28				[E]
C12E1	230.39					[D]
C12E2	274.45					[D]
C12E3	318.5					[D]
C12E4	362.55					[D]
C12E5	406.61	0.065				[D]
C12E6	450.66	0.068				[D]
	(481)	0.065		105	50	[E]
C12E7	494.72	0.069				[D]
⊗ C12E8	538.77	0.071	0.0038			#241,243
		0.08		120		[C]
		0.087		120	65	[K]
		0.07-0.1		120-125		[H]
		0.056		120	65	[E]
C12E9 (THESIT, LUBROL PX)	582.82	0.07-0.1				[H]
C12E10 (GENAPOL C-100)	~627					[H]
C12E23 (BRIJ35)	~1200	0.092		40		[H]
C13E8 (GENAPOL X-80)	~553	0.06-0.15				[H]
C13E10 (GENAPOL X-100)	~641	0.15				[H]
C13E15 (GENAPOL X-150)	~860					[H]
C14E8	567	0.0052				[E]
C16E8	595	0.00047				[E]
PLURONIC F-68	~8400					[H]
PLURONIC F-127	~8400					[H]
TWEEN 20	1228	0.059				[H]
TWEEN 80	1310	0.012		58		[H]

2.2 Phenyl Polyoxyethylenes

Name	Molwt.	cmc/mM	cmc/%	AN	Mic.size/kD	Ref.
Triton X-100	624.9	0.2		140		[C]
		0.21		140	90	[E]
		0.24	0.021			#241
		0.2-0.9		100-155		[H]
		0.3		140	90	[K], [G]
Triton X-100 hydrogenated	631	0.25				[H]

Triton X-114	537	0.2	0.028	#241
		0.35		[H]

3 Dimethylamine-N-Oxides

Name	Molwt.	cmc/mM	cmc/%	AN	Mic.size/kD	Ref.
n-Hexyl-dimethylamine-N-oxide (C6-DAO)	145.25	large		6	0.9	[F]
C7-DAO	159.27	400				[F]
C8-DAO	173.3	180		15	3	[F]
		162	2.8			#241
		175				[E]
		223				[E]
C9-DAO	187.33	50		26	5	[F]
		50.8	0.95			#241
⊕ C10-DAO	201	22	0.42			#241
		20		34	7	[F]
		9.1				[E]
		6.0				[E]
C11-DAO	215.38	6		55	12	[F]
⊕ C12-DAO (LDAO)	229.4	1.4	0.03			#241
		1.1				[C]
				69	16	[B]
		2.2		75	17.3	[F]
		1-2		76		[H]
		0.48		76	17.3	[E]
		0.23				[E]
C13-DAO	243.44	0.8		107	26	[F]

4 Cholate Derivatives

Name	Molwt.	cmc/mM	cmc/%	AN	Mic.size/kD	Ref.
Big CHAP	878.1	3.4	0.30	10		[H]
Deoxy-Big CHAP	862.1	1.1-1.4	~0.1	10		[H]
Digitonin	1229.3			5-6		[H]

5 n-Octyl Hydroxyalkylsulphoxides

Name	Molwt.	cmc/mM	cmc/%	AN	Mic.size/kD	Ref.
n-octyl-2-hydroxyethyl-sulphoxide	206	30	0.62			[C]
n-octyl-2-hydroxyethyl-sulphide						
n-octyl-rac-2,3-dihydroxy-propyl sulphide						
n-octyl-rac-2,3-dihydroxy-propyl sulfone						
n-octyl-rac-2,3-dihydroxy-						

propyl sulfoxide				
n-octyl-rac-2,3-dihydroxy-propyl sulphonate	236	23	0.54	[C]

6 Sulphobetaines

Name	Molwt.	cmc/mM	cmc/%	AN	Mic.size/kD	Ref.
SB-10	307.6	1.2	0.04			[C]
SB-12	355.6	0.12	0.004			[C]
SB-14	363.6	0.012	0.0004			[C]

7 Lipid-like Detergents

7.1 Phosphocholine Compounds

Name	Molwt.	cmc/mM	cmc/%	AN	Mic.size/kD	Ref.
Fos-Choline-8 (N-Octyl-phosphocholine)	295.4	114				[G]
Fos-Choline-9	309.4	39.5				[G]
Fos-Choline-10	323.4	11				[G]
Fos-Choline-12	351.5	1.5				[G]
Fos-Choline-14	379.5	0.12				[G]
Fos-Choline-16	407.5	0.013				[G]

Zwitter-ionic Detergents

1 Bile Acids

Name	Molwt.	cmc/mM	cmc/%	AN	Mic.size/kD	Ref.
CHAPS	614.9	~8	0.49	10		[G]
CHAPSO	630.9	~8	0.50	11		[G]

Ionic Detergents

1 Negatively Charged

Name	Molwt.	cmc/mM	cmc/%	AN	Mic.size/kD	Ref.
Sodium Dodecyl Sulfate (SDS)	288.38	2.6 (pH7.5)				[G]
		8.27 (H2O)				[G]

② = "First choice" detergents for membrane protein crystallization

⚠ = Beware! solubility < 2 x cmc!

Detergents on the Net:

Companies

- (☎ = Online-Catalog)
- ☎ Amersham
- ☎ Amresco
- ☎ Anatrace
- ☎ Boehringer-Mannheim
- ☎ Calbiochem
- Dojindo
- Mallinckrodt
- ☎ Fluka
- ☎ Hampton
- ☎ Pfanstiehl
- Pierce
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[Home](#) | [Membrane Proteins](#) | [Detergent Home-Page](#)

Enclosure

United States Patent [19]

Bauer et al.



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[54] PHARMACEUTICAL AQUEOUS FORMULATIONS CONTAINING A SPARINGLY SOLUBLE PHARMACEUTICAL ACTIVE COMPOUND WITH A SOLUBILIZING POLYMERIC AGENT

[76] Inventors: Kurt H. Bauer, 4, Im Finkeler, 79112 Freiburg/Br. 33; Markus Kiefer, 6, Unter dem Dorf, 7989 Bad Krozingen, both of Germany

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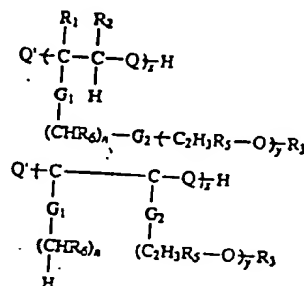
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Primary Examiner—Edward J. Webman
Attorney, Agent, or Firm—Foley & Lardner

[57] ABSTRACT

The present invention relates to pharmaceutical formulations which comprise at least one pharmaceutical active compound in combination with a polymer of the general formula I or I', in particular for intravenous administration,



(I)

Bauki-comp.

(I')

in which R_1 , R_2 , R_3 , and R_6 are identical or different and represent hydrogen and a methyl or ethyl group.

Q represents a valency, oxygen or an ester or amide bridge and Q' denotes hydrogen if Q represents a valency or oxygen, and is a hydroxyl or amino group if Q represents an ester or amide bridge.

x is an integer from 3 to 50, preferably 5 to 40, if Q is a valency or oxygen, and an integer from 3 to 1000, preferably 50 to 100, if Q is an ester or amide function, G_1 and G_2 are a valency, oxygen or an ester or amide group, it being possible for the two groups to be identical or different, n is an integer from 4 to 44, preferably 12 to 16,

y is an integer from 2 to 50, preferably 10 to 40, and R_5 is hydrogen or a lower alkyl having 1-6 C atoms.

21 Claims, No Drawings

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